REMARKS

Claims 1, 5-9, 12, 14, 15, 18-20, 22-25, and 29 are pending and under examination. Applicants gratefully acknowledge the allowance of Claim 5. Applicants have proposed to amend Claim 22 and 24 to clarify the meaning of "control cell" and to correct a minor typographical error, respectively. Applicants further request amendment of the paragraph of the specification starting at line 16 on page 7, to update the status of the identified patent applications. It is respectfully submitted that these amendments overcome the outstanding objection to the specification and the claims, and the rejection of the claims under 35 U.S.C. § 112, second paragraph; do not raise new issues of patentability; and in combination with the remarks that follow, would place the application in condition for allowance. Entry of these amendments and favorable reconsideration of the claims are respectfully requested.

The Office Action also rejected claims 1 and 18, and claims dependent therefrom, for alleged indefiniteness, as the claims do not recite "active steps if the promoter is not capable of expressing the sequence in the heart." Applicants respectfully traverse this rejection. Promoters not capable of expressing the sequence are outside the scope of the claims, and the claims need not define any step with regard to such promoters.

The final Office Action rejected claims 1, 6-9, 12, 14, 15, 18-20, 22-25 and 29 for alleged lack of enablement under 35 U.S.C. § 112, first paragraph. The rationale for the rejection is that the "art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype," and that "[w]hile the state of the art of transgenics is such that one of skill in the art would be able to produce transonic mouse comprising a transgenic DNA encoding PDGF-C, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype." The Office Action cited the opinions of two authors in two review articles, Wall, published in 1996, and Houdebine, published in 1994, (***not*** in 1997, as the Office Action stated), to support these propositions.

Applicants respectfully traverse. The fundamental flaw in the reasoning in the Office Action is that a different heart-specific promoter would qualitatively alter the nature of the invention. In other words, the Office Action makes it to appear as if the choice among similar promoters is determinative of whether the cloning/transgenic animal production would be successful or not. There is absolutely no basis to say that it is the case. In this regard, the citation or mentioning of the articles which discuss difficulties of animal cloning and the unpredictability in the "transgenic art" is irrelevant. None of these references states that the choice among similar promoters is determinative of the success of any animal cloning effort.

Firstly, the instant application was filed in 2001, quite a few years from the publication dates of the two cited articles. Between the time when these two articles were prepared and submitted for publication, and the filing date of the instant application, enormous progresses have been made in the art of transgenic animal production. For example, cloning of the famous "Dolly the Sheep" was published in early 1997. *See* Wilmut *et al.*, *Viable offspring derived from fetal and adult mammalian cells*, Nature 385, 810–813 (27 Feb 1997). In other words, the opinions expressed in the Wall and Houdebine articles, even if they support the assertion in the Office Action, do not reflect the state of the art as of the filing date of the instant application.

More importantly, the two articles do not support the assertions in the Office Action.

As discussed in applicants response to the previous Office Action, there is no question regarding the availability of many other heart-specific promoters, and that no undue experimentation is needed for obtaining a transgenic mouse. The enablement issue rests solely on whether a transgenic mouse containing a transgene under the control of another "heart-specific promoter," rather than the alpha-myosin heavy chain promoter, would be able to develop myocyte hypertrophy or heart fibrosis in the life time of the transgenic mouse. Applicants submit that the alpha-myosin heavy chain promoter is not in any way special or unique. It just happened to be the one chosen for the experiments and examples of the specification. The Office Action, on the other hand, suggests that the

alpha-myosin heavy chain promoter is unique, and has the ability that other promoters do not have in directing the development of the phenotype recited in the claims. However, it is respectfully submitted that the Office Action has failed to satisfy its initial burden of proof, and the Office Action contains no reason or explanation why or how the alpha-myosin heavy chain promoter is in any way special. The two review articles (Wall and Houdebine) cited do not support the Office Action either. There is simply no indication anywhere in Wall or Houdebine that the choice of similar promoters was an obstacle to successful animal cloning efforts, or even a determinative factor.

Wall discusses the various difficulties and factors that contributed to the inefficiency of obtaining transgenic livestock, but did not indicate in any way that these factors relate to the choice among *similar* promoters. In fact, this article emphasizes that the difficulties are due to the cost and other factors associated with farm animals, while acknowledging that the situation is quite different with the mouse ("[T]he imagination of many an animal scientist has been captivated by the success others have achieved by introducing foreign genes into mice." Second sentence, Abstract of Wall). Significantly, mouse is the animal used in the instantly claimed invention.

Similarly, there is no indication in Houdebine that any difficulties in transgenic animal production is in any way determined by the choice among similar promoters. In fact, Houdebine as early as in 1994, was quite positive on the prospects of transgenic animals, and in several places emphasized the high

successful rate when the mouse was used. For example, at page 281, first column, Houdebine stated:

> For the great majority of studies using transgenic mice, vectors working modestly are sufficient to express such or such cellular protein of interest. Although the construction of efficient vectors for expression of foreign genes in milk is not a problem sovled in all cases, there are some reasons to believe that, in future, perhaps 80% of the transgenes will work in a satisfactory manner.

In this regard, the citation by the Office Action of the passage at page 275 of Houdebine is misplaced. That passage relates to the potential role introns play in milk protein production, not the choice among similar promoters.

The Office Action further cites Niemann (1997) for the quotation that one promoter "is deleterious to the pig, the other is compatible with pig health." Applicants are unable to find the quoted text in the Niemann article. In any event, there is no indication in Niemann that promoters *having similar tissue specificity* would cause such near opposite results.

The Office Action continues to state that transgene expression is unpredictable, citing Sigmund et al., for its discussion on the randomness of gene insertion. Again, applicants respectfully submit that even this is true, it is not relevant to the current analysis, because the random nature of transgene insertion is not specific to any particular promoter choice. There is no reason to believe that promoters similar to the alpha-myosin heavy chain promoter would

cause the transgenes to behave differently while integrating in to the host genome.

Again, as previously explained, factors that influence the "unpredictability" of transgenic animal production and the level of transgene expression etc. are well known and recognized in the art. Persons with ordinary skills in the art always engage in experimentation which takes these factors into consideration. Such experimentations are considered routine.

In short, it is applicant belief that the alpha-myosin heavy chain promoter is representative of the genus of promoters capable of directing in the heart of a transgenic mouse the expression of a polynucleotide encoding a polypeptide comprising SEQ ID NO:1 or SEQ ID NO:2 and the mouse would develop the requisite symptom during its life time. The Office Action has not provided any rationale or reasonable basis to assert otherwise. The fact that applicants was able to obtain a transgenic mouse using the alpha-myosin heavy chain promoter is sufficient evidence showing that the claimed invention was enabled as of the filing date. As added proof, applicants submit, as Exhibit 1 and 2, two abstracts of articles published prior to the filing date of the instant application. The first is Griscelli et al. (1998) Hun. Gtene Ther. 9:1919-28, which shows that another heart specific promoter, the cardiac myosin light claim 2 promoter, had similar in vitro and in vivo behavior. More significantly, the second article, Honda et al. (1999) Oncogene 18:3821-30, describes a system using LTK (leukocyte tyrosine kinase) under the control of cytomegalovivras enhancers and beta-actin

promoter, where LTK was only activated in the heart and caused hypertrophy in the transgenic mice.

The claimed invention is not just a plan or invitation to try, because the invention worked with a representative promoter, and should and would work with any other similar promoter. As quoted in the Office Action, "[p]roof of enablement [of the claimed genus] will be required for other members of the claimed genus *only where adequate reasons are advanced by the examiner* to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." MPEP §2164.02 (emphasis added). In the instant case, no reasonable basis exists to doubt that the claimed genus, relative to the exemplified species, would not work or would require undue experimentation. Specifically, the examiner failed to show why and how the alpha-myosin heavy chain promoter is unique among heart-specific promoters. There is no need for the applicants to provide "evidence of nexus" between the claimed genus and the exemplified species.

In summary, it is respectfully submitted that all claims are in condition for allowance and applications earnestly solicit an early indication from the Examiner to the effect. If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029065.48487).

Respectfully submitted,

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J. D. Evans
Registration No. 26,269
Kening Li
Registration No. 44,872

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE:KL:kya
358272

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1: Hum Gene Ther. 1998 Sep 1;9(13):1919-28. Related Articles

Heart-specific targeting of beta-galactosidase by the ventricle specific cardiac myosin light chain 2 promoter using adenovi vectors.

Griscelli F, Gilardi-Hebenstreit P, Hanania N, Franz WM, Opolon P, Perricaudet M, Ragot T.

CNRS UMR 1582, Institut Gustave Roussy, Villejuif, France.

Adenoviruses are attractive vectors for gene transfer into cardiac muscle. However, their promiscuous tissue tropism, which leads to an ectopic expression of the transgene, is a considerable limitation. To restrict expre to cardiomyocytes, we have constructed two recombinant adenoviruses (A MLC2-250betagal and Ad-MLC2-2100betagal) containing the beta-galactosidase reporter gene under the control of the 250- or 2100-bp rat ventricle-specific cardiac myosin light chain-2v promoter (MLC-2v). Our vitro and in vivo data have evidenced that the 2100-bp promoter allows s beta-galactosidase activity than the 250-bp promoter and that the deleted promoter allows a weak beta-galactosidase expression in skeletal muscle-derived cells in vitro. In contrast to the in vitro results, the highly deleted 2v promoter of 250 pb conserved its heart specificity in in ovo and in viv introduced into the adenovirus genome, indicating that the specificity of t promoter is neither altered by the inverted terminal repeat nor by the enh of the Ela promoter, both of which located in the 5' flanking region of the promoter. Systemic injections of both recombinant adenoviruses into chic embryos showed beta-galactosidase expression mainly in the right ventric the heart. We have confirmed the cardiac specificity of both promoters in mammalian species after injection of both recombinant adenoviruses into heart of adult rats in vivo. The comparison of both promoters in vitro and vivo has shown that the 250-bp MLC-2v promoter is 80% less active tha 2100-bp MLC-2v promoter and has enabled us to conclude that the MLC promoter of 2100 bp is the most appropriate for efficient expression of a reporter gene or a therapeutic cardiac gene (e.g., SERCA2a or minidystro gene).

PMID: 9741430 [PubMed - indexed for MEDLINE]

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1: Oncogene. 1999 Jul 1;18(26):3821-30. Related Articles

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Heart-specific activation of LTK results in cardiac hypertrop cardiomyocyte degeneration and gene reprogramming in transgenic mice.

Honda H, Harada K, Komuro I, Terasaki F, Ueno H, Tanaka Y, Kawamura K, Yazaki Y, Hirai H.

Third Department of Internal Medicine, Faculty of Medicine, University Tokyo, Japan.

Leukocyte tyrosine kinase (LTK) is a receptor-type protein tyrosine kinas belonging to the insulin receptor superfamily. To elucidate its biological we generated transgenic mice expressing LTK under the control of cytomegarovirus enhancer and beta-actin promoter. The transgenic mice exhibited growth retardation and most of the transgenic mice died within several months after birth. Interestingly, although LTK was expressed in major organs, the activation (tyrosine-phosphorylation, kinase activity, ar multimerization) of LTK was observed selectively in the heart, where LT localized on intracellular membrane, presumably on endoplasmic reticulu Echocardiography showed that the transgenic heart underwent severe con hypertrophy, which resulted in reduced cardiac output, low blood pressur increased heart rate. Histological examination of the heart exhibited focal degeneration of cardiomyocytes. These histological changes were consid be due to apoptosis, based on the finding that the sarcolemmas of the degenerative cardiomyocytes were well preserved. In addition, expressio fetal genes, such as atrial natriuretic peptide and skeletal alpha-actin, was markedly induced in the transgenic heart. These results indicate that a cer tissue-specific mechanism of activating LTK exists in the heart and that t activated LTK resulted in cardiac hypertrophy, cardiomyocyte degenerati gene reprogramming. These findings will provide novel insights into the activating mechanism and biological role of LTK in vivo.

PMID: 10445845 [PubMed - indexed for MEDLINE]